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The Role of Estrogens as a Risk Factor for Stroke in Postmenopausal Women

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The estrogen component in oral contraceptives is generally thought to increase the risk of stroke in users as compared with controls. If this were true, an increased risk for stroke also should be seen among postmenopausal women using estrogens as compared with nonusers. To test this hypothesis, the charts of 198 postmenopausal patients who had had strokes were compared with those of 396 controls for estrogen use and for the associated risk factors of diabetes, hypertension and coronary artery disease. The difference between estrogen use in the study population versus controls proved not significant, and the use of estrogens did not significantly influence the distribution of the above risk factors. We concluded that the use of estrogens in physiological replacement doses does not increase the risk of stroke in postmenopausal women.

THE COLLABORATIVE GROUP for the Study of Strokes in Young Women in 1973 showed that the use of oral contraceptives greatly increases the risk of stroke in users compared with that in normal controls. This initial observation provoked further inquiry into what effects these steroid compounds might have in young women to cause a disease which is usually seen in much older patients. Oral contraceptives contain both estrogens and progestational compounds. Many hypothesized at the time our study was begun that the harmful component was probably estrogen. We reasoned that if this explanation were correct, it could be shown that postmenopausal women taking oral estrogen preparations are at greater risk for the development of stroke than postmenopausal women who do not take estrogens. This study investigates the role of estrogens as an independent risk factor for stroke in postmenopausal women.

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Patients and Methods

The Kaiser Foundation Health Plan provided names and identifying data for all women over the age of 45 years who were discharged from the Northern California Kaiser Foundation Hos-

pitals with a diagnosis of stroke during the years 1972 through 1974. We chose to include only stroke patients discharged from the San Francisco, Redwood City, South San Francisco, Hayward and Santa Clara facilities in the study, as these provided an adequate number of cases representing a broad spectrum of socioeconomic populations. (These facilities serve urban, suburban and rural, industrial and white-collar populations.)

The charts of potential subjects were first reviewed by the neurologist in the team. Only those patients whose records supported the diagnosis of occlusive cerebrovascular disease referable to a specific artery were included in the study. Cases of intracerebral hematoma were excluded, as were such vague diagnoses as "cerebrovascular insufficiency" and "dizziness." The data examined included the history, physical examination and all verifying laboratory x-ray studies, including the results of angiography when available. The distinction between lesions of the internal carotid artery and lesions of its branches—middle and anterior cerebral—was made by either angiographic data or a documented history of transient ischemic attack or attacks in an internal carotid distribution preceding the fixed deficit. The inpatient and outpatient charts for these cases were reviewed by the two physician investigators for the use of estrogens. In addition, the charts were reviewed for evidence of three other recognized risk factors for cerebral and cardiovascular disease, diabetes, hypertension and coronary artery disease. (We attempted to examine smoking histories, but there was so much variation in the amount of information recorded that this was not feasible.)

The criteria for these risk factors were as follows:

- Patients were considered to have diabetes if that diagnosis had been made by their treating physicians or if repeated fasting blood sugar measurements on the chart exceeded our normal laboratory value (110 mg per dl) at the time of the study.
- Patients were considered to have hypertension if repeated blood pressure readings on the chart consistently exceeded 140/90 mm of mercury, or if the attending physician had diagnosed the patient as hypertensive (to include patients who may have had lower blood pressure readings because of antihypertensive medication).

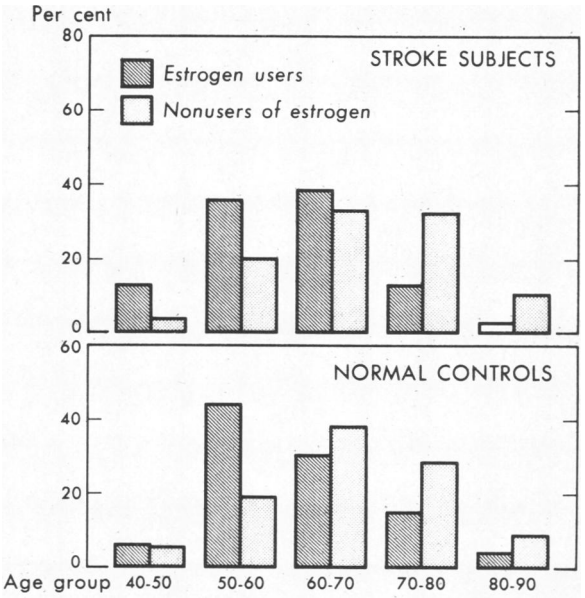

Figure 1.—Age distribution of estrogen users versus nonusers in postmenopausal women who had had strokes and in normal controls.

- Patients were considered to have coronary artery disease if their clinical histories included myocardial infarction, angina pectoris or unexplained cardiac arrhythmias, or if findings on electrocardiograms were interpreted as consistent with coronary artery disease.

In the chart analysis for estrogen use, the specific preparation and duration of use were determined. The subject cases had to be taking estrogens at the time of the stroke, and the control cases had to be using estrogens at the time the subject case to whom they were matched had the stroke.

Some subscribers to the Kaiser Foundation Health Plan obtain some care outside the plan. We therefore wanted to assess if inpatient and outpatient charts used for our study contained complete information on the patients' medical and drug histories. To this end, we mailed questionnaires to our patients covering the information we were seeking in our chart review. Of the 215 questionnaires sent out, 84 were returned, and these showed excellent correlation with the data on the charts.

The subjects were then matched by age and geographic location with normal controls randomly selected from the data bank of the Kaiser Foundation Health Plan. Normal controls were patients who had not had strokes. The criteria for age-

TABLE 1.—*Treatment Histories for Use of Estrogen Medications Other Than Premarin**

Medication	Stroke Patients (8) Dose (mg)	Stroke Patients (8) Duration (years)	Controls (5) Dose (mg)	Controls (5) Duration (years)
Esterified estrogens (Amnestrogen)	0.3	2	None	
	0.625	10		
Ethinyl estradiol and methyltestosterone (Gynetone)	0.2	1	0.2	2
	0.2	2		
Ethinyl estradiol	0.05	5	0.02	10
	0.05	10	0.05	8
Diethylstilbestrol (DES)	0.05	3	None	
	0.05	3		

*Premarin (conjugated estrogens)

TABLE 2.—*Prevalence of Risk Factors Associated With Stroke in 198 Postmenopausal Women Who Had Had Strokes Versus 396 Controls*

Risk Factor	Stroke Patients (percent)	Controls (percent)
Hypertension	55	41
Diabetes	26	5
Coronary artery disease	47	11

matching was that the age of the controls should be within five years of the age of the subject. The criteria for geographic matching was that the control should live in the same city as the subject. For each subject, we obtained two age- and geographic-matched controls. Despite four computer searches, matching controls were not found for 17 patients, who were therefore excluded from the final tabulation. Without exception, the patients who could not be matched with controls were in the 80- to 90-year age group and lived in small communities; none were taking estrogens. A total of 198 subjects and 396 controls remained. The outpatient medical records of the controls were reviewed to confirm that these controls had not had strokes, to assess the same risk factors that were determined for the subjects (diabetes, hypertension and coronary artery disease) and to assess the use of estrogens. The incidence of risk factors was then compared in the subjects and their age- and geographic-matched controls. The data collected from both subjects and controls came from the outpatient charts.

Results

While the age distribution was wide, most of the 198 subjects in our study were between 50 and 80 years of age (Figure 1).

The specific neurological diagnoses recorded for our stroke cases were as follows: (1) occlusion of one of the middle cerebral arteries, 64 percent; (2) occlusion of one of the internal carotid arteries, 22 percent; (3) occlusion in the vertebrobasilar arterial system, 7 percent; (4) lacunar infarction, 5 percent, and (5) occlusion of one of the anterior cerebral arteries, 2 percent.

Of the estrogen preparations used by our subject patients, conjugated estrogens (Premarin) were used by all but eight; and among those using Premarin, all but two were taking either 0.625 mg or 1.25 mg doses. These latter two had been taking 0.3 mg for five years and 2.5 mg for two years, respectively, up to the time of the stroke. The average duration of use of the 0.625 mg dose was 6.85 years and of the 1.25 mg dose was 5.9 years preceding the stroke.

Among the controls who used Premarin, all but five patients were taking 0.625 mg or 1.25 mg per day. Of these five, four patients had taken 0.3 mg of Premarin daily for an average duration of three years preceding the time of stroke in the matched subject patients, and one patient had been taking 3.0 mg daily for a year. In the remaining controls, a third had been taking a 0.625 mg dose of Premarin for an average duration of 7.6 years, and two thirds had been taking 1.25 mg for an average of 7.15 years preceding the time of stroke in the matched subject patients. These doses of conjugated estrogens represent physiological doses for menopausal replacement therapy. The treatment histories of stroke patients and controls taking medications other than Premarin are listed in Table 1.

Of the patients who had had strokes, 20.7 percent had been taking estrogens; in the control group, 18.4 percent were taking estrogens. This difference was not significant ($x^2 = 0.4396$). The relative risk of stroke was estimated (by the relative odds method) to be 1.16 times as great in estrogen users as nonusers, with 95 percent confidence limits[2] of 0.75 and 1.77.

As expected, those risk factors which have been associated repeatedly with stroke were more prevalent in our stroke population than in the controls (Table 2).

We endeavored to see if the use of estrogens influenced the distribution of the risk factors by reanalyzing our data with cases and controls pooled. Hypertension was found in 45.6 percent of the estrogen users and 46 percent of the non-

users. Coronary artery disease was found in 22.8 percent of the estrogen users and in 22 percent of the nonusers. Diabetes was found in 6.1 percent of the estrogen users and 14 percent of the nonusers. Because of this last observation, the relative risk of stroke in the estrogen users and nonusers was recalculated after the factor of diabetes had been removed. After removal of patients with diabetes from the population, the percentage of stroke patients using estrogens was 24.0 percent and the percentage of control patients using estrogens was 19.3 percent. This difference was not significant ($x^2 = 1.43$). (The relative risk of stroke in estrogen users compared with nonusers was estimated to be 1.32, with 95 percent confidence limits of 0.84 and 2.09.)

Our data show that the risk factor of use of estrogens in our patients who had had strokes was no different from that among users of estrogens in the population of matched controls. In addition, the risk factors of hypertension, coronary artery disease and diabetes coupled with estrogen use did not increase the risk of stroke above that associated with these factors alone.

Discussion

This study was preceded by a large body of medical literature linking oral contraceptives with cardiovascular disease. In addition to their 1973 study,[1] which provided the stimulus for this research, the Collaborative Group for the Study of Stroke in Young Women also reported in 1975[3] that oral contraceptives are an independent risk factor and do not act by augmenting the effect of other risks such as hypertension, smoking or migraine.

Mann and associates[4] reported in 1975 that oral contraceptive use was considerably more frequent in women who had nonfatal myocardial infarctions. This risk factor appeared to prevail even in the absence of cigarette smoking, hypertension, diabetes, hypercholesterolemia, toxemia of pregnancy or obesity. The risk of death from myocardial infarction in their studies was estimated to be 2.8 times greater in current users of oral contraceptives who were 30 to 39 years of age and 4.7 times greater in current users who were 40 to 44 years of age.

The Stanford Three-Community Study in 1976[5] described a differential effect of oral contraceptives versus pure estrogens on cardiovascular risk factors. The study found a more profound elevation of plasma triglyceride and a greater degree of hypertension in users of combination oral contraceptives than in users of pure estrogens, and that this difference correlated with the amount of progesterone and not the amount of estrogen in the preparation.

The physiological doses of estrogens used for menopausal replacement therapy are from a half to a sixth as potent as the estrogens contained in the oral contraceptives.

These physiological doses are, however, the same dosages which have been implicated as carcinogenic for endometrial carcinoma and as a form of protection in postmenopausal women against osteoporosis.

The purpose of this study was to find if there was an increased risk of stroke in women after menopause who were taking physiological doses of estrogens for the postmenopausal syndrome compared with women who did not use these hormones.

After we had completed our independent study but before its publication, Pfeffer and van den Noort[6] reported the results of a study similar to ours conducted among postmenopausal women aged 58 through 95 years in a California retirement community. The findings of that study agree with ours in that the use of estrogens in physiological replacement dosages did not increase the risk of stroke in postmenopausal women.

The Boston Collaborative Drug Surveillance Program[7] reported in 1976 that the regular use of estrogens after menopause did not increase the risk of nonfatal myocardial infarction. Of 336 patients who had sustained myocardial infarctions, 2.4 percent were regular users of estrogens; 4.9 percent of the controls were regular users of estrogens as well. The Boston study data do not support the suggestion that estrogen use has a protective effect against nonfatal myocardial infarctions, but rather that estrogen use has no effect.

The incidence of estrogen replacement among our patients was four times greater than that of the Boston study. Similarly, the study of Pfeffer and van den Noort[6] detected a much higher percentage of women receiving estrogen replacement therapy than that found in the Boston study. We cannot readily explain this difference except to note that the differences in style of practice, patient demand and, possibly, socioeconomic levels

may explain the higher percentage of estrogen use in our population.

Many factors must be evaluated when deciding if a particular patient should receive estrogen replacement during menopause. The potential risk of endometrial carcinoma is an important factor, as well as the potential adverse effect of estrogens on coexistent hypertension. Nonetheless, some postmenopausal women require estrogen replacement therapy to allow them to function adequately.

The benefit/risk factor of estrogen replacement therapy must always be scrutinized. The results of this study show that use of estrogens in physiological replacement doses is not associated with increased risk of stroke in postmenopausal women.

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